

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 605 578 B1

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the grant of the patent:  
10.01.1996 Bulletin 1996/02

(51) Int. Cl.<sup>6</sup>: A61K 9/00, A61K 9/12

(21) Application number: 92920611.8

(86) International application number: PCT/GB92/01749

(22) Date of filing: 23.09.1992

(87) International publication number: WO 93/05765  
(01.04.1993 Gazette 1993/09)

### (54) PRESSURISED AEROSOL COMPOSITIONS

UNTER DRUCK AEROSOLZUSAMMENSETZUNGEN  
COMPOSITIONS POUR AEROSOLS SOUS PRESSION

(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL  
PT SE

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(30) Priority: 25.09.1991 GB 9120396  
28.09.1991 GB 9120675  
19.11.1991 GB 9124661  
14.02.1992 GB 9203212

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(43) Date of publication of application:  
13.07.1994 Bulletin 1994/28

(56) References cited:  
EP-A- 0 372 777 WO-A-87/05211

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Remarks:

Consolidated with 92308657.3/0534731 (European  
application No./publication No.) by decision dated  
12.10.94.

EP 0 605 578 B1

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**Description**

This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquefied chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all application of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unrepeatable dosing.

The use of hydrofluorocarbons as aerosol propellants has also been suggested. However, considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofluoroalkanes and capable of stabilising medicaments suspensions.

Surprisingly, we have found that certain polymers are both soluble in the aerosol propellants and capable of stabilising medicament compositions.

Thus, according to the invention, we provide a pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

The polymer may be a homopolymer, that is the polymer consists of the same recurring structural units, or it may be a copolymer, that is the polymer contains recurring units in addition to either amide containing units or carboxylic acid ester units. The polymer may also be a copolymer of amide containing units and carboxylic acid ester units. Such copolymers may be either block copolymers or random copolymers.

We prefer polymers which include recurring structural units containing an amide group. We particularly prefer the amide containing unit to be 1-ethylene-pyrrolidin-2-one. We especially prefer the polymer to be a homopolymer containing recurring 1-ethylene-pyrrolidin-2-one, that is polyvinylpyrrolidone.

In general, we have found that polyvinylpyrrolidones having a wide range of average molecular weights give acceptable suspensions. Although polymers can be characterised by their weight average molecular weights, viscosity average molecular weights or number average molecular weights, it is more usual to characterise polymers, in particular polymers such as polyvinylpyrrolidone, by K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellulosechemie*, 1932, 13, 58-64 and 71-74). In particular we prefer the polymer to have a K value of from 10 to 150, more preferably 15 to 120. Particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125.

Suitable polymers containing carboxylic acid ester containing recurring structural units include polyvinylacetate and copolymers of vinyl acetate and vinyl pyrrolidone, that is polyvinylpyrrolidone/vinyl acetate copolymer. We have found that polyvinylacetate with a weight average molecular weight of 250,000 gives particularly stable suspensions.

Other polymers that may be mentioned include acrylic acid/methacrylic acid ester copolymers, especially those in which the methyl and ethyl ester groups have been replaced with a low content of trimethylammoniummethyl groups, preferably at a ratio of 1:20, especially at a ratio of 1:40. We have found that such copolymers having a weight average molecular weight of 150,000 give stable suspensions.

The amount of polymer in the composition will depend on the active ingredient to be dispersed, its concentration and the particular polymer selected. However, in general the amount of polymer is from 0.00001 to 10% w/w, more preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w.

The compositions may, in addition to the polymer, contain other excipients, in particular excipients intended to improve valve lubrication and excipients to modify flavour. Particular lubricants that may be mentioned include polyethoxylated compounds, especially polyethylene glycol. We prefer polyethylene glycol having a mean molecular weight of from 200 to 3000, preferably 400 to 2000, eg 1500. Other polyethoxylated compounds that may be used as lubricants include polysorbates, eg polysorbate 80, and alkyl aryl polyether alcohols, eg tyloxapol. Other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofluorocarbons and esters of medium chain fatty acids. The amount of lubricant in the composition will depend on the other components of the composition, the active ingredient, the nature of the valve, etc. In general, we prefer a concentration of 0.01 to 4% w/w and more preferably 0.1 to 2% w/w.

Flavour modifying excipients that may be added to the composition include peppermint oil, menthol, Dentomint (Dentomint is a tradename), saccharin and saccharin sodium. When the flavour modifying excipient is a solid, preferably it is micronised. The concentration will depend on the individual composition and the flavour modifying excipient. In general, we prefer a concentration of 0.005 to 4% w/w; more preferably 0.01 to 1% w/w.

By the term 'hydrofluoroalkane' we mean a compound of general formula



5 in which x is an integer from 1 to 3, y+z=2x+2 and y and z are both at least 1.  
 Particular hydrofluoroalkanes of interest are  $CF_3CFH_2$  (Propellant 134a),  $CH_3CHF_2$  (Propellant 152a) and  $CF_3CHFCF_3$  (Propellant 227). We particularly prefer compositions including propellant 227.

In general the vapour pressure of the propellant mixture should be in the range suitable and permitted for aerosol propellants. The vapour pressure may be varied by mixing one or more hydrofluoroalkanes and/or some other suitable 10 vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psig, more preferably 40 to 80 psig, eg about 60 psig.

In certain cases we have found it advantageous to add to the compositions excipients capable of increasing the 15 solubility of the polymer or of other excipients, in the propellant. In general we have found that the polymers selected have a solubility in the propellant of at least 0.0001% w/w, preferably at least 0.001% w/w, particularly 0.01% w/w and especially 0.1% w/w. Excipients capable of increasing the solubility of the polymer include liquid excipients which are more polar than the liquefied propellant, where polarity is defined in terms of relative Kauri butanol values, as described 20 in European patent application 0 372 777. Particular excipients that may be mentioned include alcohols eg ethanol and isopropanol. However, in contrast to the teaching of EP 0 372 777, we have found that only very small quantities of such excipients are required. In particular we have found that good compositions can be prepared in propellant 134a with polyvinylpyrrolidone as polymer with a variety of active ingredients and less than 10% w/w, preferably less than 5% w/w, more preferably less than 2% w/w, eg 0.2% w/w ethanol.

Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments 25 which are conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone propionate, budesonide and iprednol, and bronchodilators, eg salbutamol, reproterol, terbutaline, formoterol, pirbuterol, isoprenaline, salmeterol, fenoterol and salts thereof, and anticholinergic agents such as ipratropium bromide, 30 oxitropium bromide and atropine and combinations of two or more of these agents, eg a combination of a prophylactic agent with a bronchodilator, eg sodium cromoglycate with salbutamol.

Other medicaments that may be mentioned include antihistamines, eg clemastine, pentamidine and salts thereof, 35 acetyl- $\beta$ -methylcholine bromide, peptide hormones such as insulin and amylin, bradykinin antagonists,  $PLA_2$  inhibitors, PAF antagonists, lipoxygenase inhibitors, leukotriene antagonists, CNS active drugs, such as NMDA antagonists, glutamate antagonists, CCK agonists and antagonists; macrolide compounds including FK 506, rapamycin, cyclosporin and structurally related compounds, vitamins, vaccines, eg MMR vaccine and polio vaccine and vectors for gene therapy, eg 40 plasmids containing genes intended to correct genetic disorders such as cystic fibrosis.

Where the medicament is intended for delivery to the lung, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the medicament is 45 preferably in a form having a mass median diameter of from 0.01 to 10  $\mu m$ , more preferably from 0.1 to 4  $\mu m$ , eg about 2 or 3  $\mu m$ .

The amount of medicament in the composition will depend on the nature of the active ingredient and the condition to be treated. However, the composition preferably comprises from 0.01 to 15% w/w, preferably from 0.1 to 10% w/w, and most preferably from 0.5 to 5% w/w medicament.

According to a further aspect of the invention there is provided a method of producing a pressurised aerosol composition 50 as herein described, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

In particular, the compositions may be produced by cold fill or pressure fill techniques. In cold filling, the ingredients are placed in a cooled mixing vessel, cooled liquefied propellant added and a dispersion produced by vigorous stirring. Alternatively, a slurry may be prepared of the ingredients in a portion of cooled liquid propellant and the remainder of 55 the liquefied propellant added under vigorous stirring. Aliquots of the dispersed composition are then filled into cooled aerosol cans and sealed with a suitable valve, eg a metering valve.

In pressure filling, the ingredients are placed in a pressure vessel, liquefied propellant added under pressure through a valve and a dispersion of the ingredients in the liquefied dispersed composition are then filled, under pressure, through the valve into suitable cans provided with appropriate valves, eg metering valves.

55 The compositions according to the invention are advantageous in that the solubility of the polymer is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve.

The compositions of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may

be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

The performance of the compositions according to the present invention can be assessed using the following test procedures:

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### 1. Settling times

A glass bottle containing the composition is gently shaken five times and then stood upright. The time interval between standing the bottle upright and the first appearance of flocculation or separation of powder in the propellant 10 determined ( $S_1$ ). Timing is continued until complete separation, defined as when three lines of standard newspaper print can be read through the propellant from the top or bottom, depending on whether the active ingredient floats or sinks ( $S_2$ ). In some compositions, complete separation does not occur. For these compositions, a turbidity factor ranging from 1 to 5 is determined, 1 denoting that a small proportion of the active ingredient is suspended and 5 denoting that the majority of the active ingredient is suspended.

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### 2. Dispersion Tests

Dispersion testing on compositions formulated in cans having a metering valve can be assessed using a glass multistage liquid impinger, eg of the type described by J.H. Bell *et al.*, *J. Pharm. Sci.*, 1971, **60**(10), 1559.

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### 3. Lubrication

The lubricating effects of the composition can be assessed by filling the formulation into a can and closing the can with a modified metering valve from which the return spring has been removed. The stem of the valve is subjected to a 25 compression force and the reading recorded in Newtons. This gives a measure of the lubricating efficacy of the composition.

### 4. Dose uniformity

30 Dose uniformity is assessed by discharging a metered dose aerosol can containing the composition into a filter tube which has sufficient air flowing through it to entrain all the dose. The tube is washed out with a suitable solvent and the amount of medicament assayed. The medicament entrained on the mouthpiece is also washed off and assayed. The variation of dose evaluated throughout the life of the can is a measure of dose uniformity. In a variation of this test, dose uniformity after standing can be assessed by shaking the aerosol can, allowing to stand for a predetermined time and 35 assessing dose in the manner described above.

### 5. Caking potential

40 Compositions to be assessed are filled into plastic coated glass bottles. The assessment is carried out by allowing the samples to be stored for a period of time in order that complete sedimentation and compaction of the powder mass can take place, eg 3 months. After that period, the glass bottles are shaken by gentle twisting of the hand to totally invert the bottles. The number of bottle inversions required to completely resuspend the drug is noted. The number gives a measure of the degree of compaction of the composition. Since ease of drug particle redispersion is essential for dose uniformity, any composition requiring more than 5 shakes suggests possible problems in long-term storage.

45 The invention will now be illustrated, but in no way limited, by the following Examples.

### Examples

### Method

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The required amounts of micronised active ingredient, suspending agent and other excipients, were weighed into plastic coated glass bottles and crimped with an appropriate valve. The desired amount of liquefied propellant was then transferred using a transfer button and the contents of the bottle sonicated to ensure thorough mixing. Unless otherwise stated, the fill volume for the bottles was 20 ml.

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**Materials****Active ingredients**

5 All active ingredients were micronised. In general, the active ingredients were anhydrous, although nedocromil sodium and sodium cromoglycate were used in their equilibrium hydrated form which each contain about 10% w/w water at room temperature.

**Polyethyleneglycols (PEG)**

10 The average molecular weight of the polyethyleneglycol used is indicated by the number 200, 400, etc following PEG.

**Halocarbon oil**

15 Halocarbon oil is the proprietary name given to a series of high molecular weight fully halogenated chlorofluorocarbons of chlorotrifluoroethylene telomers obtainable from Halocarbon Products Corporation, New Jersey, USA.

**Miglyols**

20 **Miglyol® neutral oils**

Miglyol® neutral oils are esters of medium chain fatty acids and are sometimes referred to as fractionated coconut oils. Miglyol is a trademark of Hüls AG. The following oils were used.

25 **Miglyol® 810**

A triglyceride of fractionated C<sub>8</sub>/C<sub>10</sub> coconut oil fatty acids classified by the CTFA as caprylic/capric triglyceride. It meets the requirements of the British Pharmacopoeia 1988 for the monograph "Fractionated Coconut Oil". It is a low viscosity oil of neutral taste and smell, with a turbidity point below 0°C.

30 **Miglyol® 829**

A glyceryl ester of fractionated C<sub>8</sub>/C<sub>10</sub> coconut fatty acids linked to succinic acid and is classified by the CTFA as caprylic/capric/diglyceryl succinate. It has a turbidity point below -30°C, is soluble in alcohol, has a viscosity of approximately 250 mPa.s and a density of approximately 1.

**Miglyol® 840**

40 A propylene glycol diester of saturated vegetable fatty acids with C<sub>8</sub>/C<sub>10</sub> chain lengths, classified by the CTFA as propyleneglycol dicaprylate/dicaprate. It meets the requirements of the German Pharmacopoeia, DAR9, 1st supplement, for the monograph "Propyleneglycoloctanoatodecanoate". It has a turbidity point below -30°C and is soluble in 90% ethanol.

**Polyvinylpyrrolidones**

45 All polyvinylpyrrolidones used were essentially linear homopolymers formed by the free radical polymerisation of N-vinylpyrrolidone. PVP(K29/32), PVP(K90), PVP(K120), PVP(C15) and PVP(C30) refer to the polyvinylpyrrolidones obtainable from GAF Chemical Corporation and sold under the Trade Mark PLASDONE®. PVP/17PF refers to KOL-LIDON 17PF, a polyvinylpyrrolidone available from BASF (KOLLIDON is a registered Trade Mark).

50 The manufacturing processes for polyvinylpyrrolidone and the other polymers used herein produce polymer mixtures containing molecules of unequal chain length and thus different molecular weights. Such polymers are usually characterised by their K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellulosechemie*, 1932, 13, 58-64 and 71-74). The polymers can also be characterised by their average molecular weights (M<sub>w</sub>), viscosity average molecular weights (M<sub>v</sub>) and number average molecular weights (M<sub>n</sub>).

Characterising data for the polyvinylpyrrolidones used were as follows:

|    | K         | $\bar{M}_w$ | $\bar{M}_v$ | $\bar{M}_n$ |
|----|-----------|-------------|-------------|-------------|
| 5  | PVP 17 PF | 15-18       | 9000        | -           |
|    | K29/32    | 29-32       | -           | -           |
| 10 | K90       | 94±6        | 1,280,000   | 63000       |
|    | K120      | 120±5       | 2,800,000   | 1,450,000   |
|    | C15       | 17±1        | 10500       | 7000        |
|    | C30       | 30.5±1      | 62500       | 3800        |
|    |           |             |             | 16500       |

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#### Polyvinylpyrrolidone/vinylacetate copolymers

20 Polyvinylpyrrolidone/vinylacetate copolymers are obtainable from GAF Chemical Corporation. The E- and I- series of PVP/VA copolymers were supplied as 50% solutions in ethanol and isopropanol respectively. S-630 refers to the white, spray dried polymer of PVP/VA having the characteristics set out below. Characterising data for PVP/VA used:

|    |        | K value | VP/VA ratio |
|----|--------|---------|-------------|
| 25 | PVP/VA | S-630   | 30-50       |
|    |        | E-535   | 30-50       |
| 30 |        | I-535   | 25-35       |
|    |        | E-335   | 25-35       |
|    |        |         | 60/40       |
|    |        |         | 50/50       |
|    |        |         | 50/50       |
|    |        |         | 30/70       |

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#### Acrylic acid/methacrylic acid ester copolymers

40 The acrylic acid/methacrylic acid ester copolymers used were copolymers synthesized from acrylic and methacrylic acid ethyl and methyl esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the neutral (meth)acrylic acid esters is 1:40. The weight average molecular weight is approximately 150000. The polymer used was EUDRAGIT RS PM, obtainable from Röhn Pharma GmbH. (EUDRAGIT is a registered Trade Mark).

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**Polyvinylacetate**

The polyvinylacetate used had a weight average molecular weight of about 26,000.

5    **A. Compositions containing polyvinylpyrrolidone and propellant 227**

The following active ingredients were formulated at the concentration shown with PVP in propellant 227 **PLASDONE C30** (**PLASDONE** is a registered Trade Mark of GAF Chemicals Corporation).

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| a) with 0.05% w/w PVP(C-30) |  |          |
|-----------------------------|--|----------|
| 1.                          | Terbutaline sulphate                   | 5mg/ml   |
| 2.                          | Beclomethasone dipropionate            | 5mg/ml   |
| 3.                          | Salbutamol sulphate                    | 4mg/ml   |
| 4.                          | Fluticasone propionate                 | 4mg/ml   |
| 5.                          | Reproterol hydrochloride               | 10mg/ml  |
| 6.                          | Fenoterol hydrobromide                 | 4mg/ml   |
| 7.                          | Sodium cromoglycate                    | 10mg/ml  |
| 8.                          | Sodium cromoglycate                    | 50mg/ml  |
| 9.                          | Ipratropium bromide                    | 0.8mg/ml |
| 10.                         | Pentamidine isoethionate               | 4mg/ml   |
| 11.                         | Clemastine                             | 4mg/ml   |
| 12.                         | Acetyl- $\beta$ -methylcholine bromide | 10mg/ml  |
| 13.                         | Budesonide                             | 4mg/ml   |

| b) with 0.1% w/v PVP(17PF) |                        |        |
|----------------------------|------------------------|--------|
| 1.                         | Fenoterol hydrobromide | 4mg/ml |
| 2.                         | Terbutaline sulphate   | 5mg/ml |
| 3.                         | Salbutamol sulphate    | 4mg/ml |

| c) with 0.025% w/v PVP(C30) |           |         |
|-----------------------------|-----------|---------|
| 1.                          | Tipredane | 10mg/ml |

## B. Compositions containing polyvinylpyrrolidone/vinyl acetate copolymer in propellant 227

The following active ingredients were formulated in propellant 227 at the concentrations shown.

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| a) with 0.05% w/v PVP/VA S-630 |  |          |
|--------------------------------|--|----------|
| 1.                             | Terbutaline sulphate                   | 5mg/ml   |
| 2.                             | Beclomethasone dipropionate            | 5mg/ml   |
| 3.                             | Salbutamol sulphate                    | 4mg/ml   |
| 4.                             | Fluticasone propionate                 | 4mg/ml   |
| 5.                             | Reproterol hydrochloride               | 10mg/ml  |
| 6.                             | Fenoterol hydrobromide                 | 4mg/ml   |
| 7.                             | Sodium cromoglycate                    | 10mg/ml  |
| 8.                             | Sodium cromoglycate                    | 50mg/ml  |
| 9.                             | Ipratropium bromide                    | 0.8mg/ml |
| 10.                            | Acetyl- $\beta$ -methylcholine bromide | 10mg/ml  |
| 11.                            | Budesonide                             | 4mg/ml   |

## b) with 0.025% w/v PVP/VA S-630

|    |           |         |
|----|-----------|---------|
| 1. | Tipredane | 10mg/ml |
|----|-----------|---------|

## C. Compositions containing PVP or PVP/VA, propellant 227 and polyethylene glycol

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The following active ingredients were formulated in propellant 227 at the concentration shown with 0.5% w/v PEG600.

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| a) with 0.05% w/v PVP(C30) |                          |         |
|----------------------------|--------------------------|---------|
| 1.                         | Salbutamol sulphate      | 4mg/ml  |
| 2.                         | Sodium cromoglycate      | 50mg/ml |
| 3.                         | Reproterol hydrochloride | 10mg/ml |

| b) with 0.05% w/v PVP/VA S-630 |                          |         |
|--------------------------------|--------------------------|---------|
| 1.                             | Salbutamol sulphate      | 4mg/ml  |
| 2.                             | Sodium cromoglycate      | 50mg/ml |
| 3.                             | Reproterol hydrochloride | 10mg/ml |
| 4.                             | Budesonide               | 4mg/ml  |

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| c) with 0.1% w/v PVP(17PF) |                        |        |
|----------------------------|------------------------|--------|
| 1.                         | Terbutaline sulphate   | 5mg/ml |
| 2.                         | Fenoterol hydrobromide | 4mg/ml |

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**D. Compositions containing acrylic acid/methacrylic acid ester copolymers and propellant 227**

The following active ingredients were formulated at the concentration shown with 0.1% w/v **EUDRAGIT RS**  
15 (EUDRAGIT is a Trade Mark of Röhm Pharma GmbH) in propellant 227.

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| a)  |                                |          |
|-----|--------------------------------|----------|
| 1.  | Terbutaline                    | 5mg/ml   |
| 2.  | Beclomethasone dipropionate    | 5mg/ml   |
| 3.  | Salbutamol sulphate            | 4mg/ml   |
| 4.  | Fluticasone                    | 4mg/ml   |
| 5.  | Reprotoxol hydrochloride       | 10mg/ml  |
| 6.  | Fenoterol                      | 4mg/ml   |
| 7.  | Sodium cromoglycate            | 10mg/ml  |
| 8.  | Ipratropium bromide            | 0.8mg/ml |
| 9.  | Clemastine                     | 4mg/ml   |
| 10. | Acetyl-β-methylcholine bromide | 10mg/ml  |

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| b) compositions including 0.5%w/w PEG 600 |                             |         |
|---|-----------------------------|---------|
| 11.                                       | Beclomethasone dipropionate | 5mg/ml  |
| 12.                                       | Sodium cromoglycate         | 50mg/ml |
| 13.                                       | Reprotoxol hydrochloride    | 10mg/ml |
| 14.                                       | Fenoterol hydrobromide      | 4mg/ml  |

## E. Compositions in propellant 134a

The following active ingredients were formulated at the concentration shown in propellant 134a.

|    |    |  |                                  |
|----|----|--|----------------------------------|
| 5  | 1. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 10 | 2. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.1% w/w<br>10.0% w/w |
| 15 | 3. | Nedocromil sodium<br>PVP(C30)<br>ethanol | 20mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 20 | 4. | Nedocromil sodium<br>PVP(C30)<br>ethanol | 20mg/ml<br>0.1% w/w<br>10.0% w/w |
| 25 | 5. | Tipredane<br>PVP/VA S-630<br>ethanol     | 10mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 30 | 6. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.25% w/w<br>5.0% w/w |
| 35 | 7. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.5% w/w<br>5.0% w/w  |

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8. Nedocromil sodium 20mg/ml  
PVP/VA S-630 0.1% w/w  
ethanol 5.0% w/w

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9. Nedocromil sodium 20mg/ml  
PVP/C30 0.25% w/w  
ethanol 5.0% w/w

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10. Nedocromil sodium 20mg/ml  
PVP(C30) 0.5% w/w  
ethanol 5.0% w/w

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11. Tipredane 10mg/ml  
PVP(C30) 0.1% w/w  
PEG 600 0.5% w/w  
ethanol 5.0% w/w

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12. Tipredane 10mg/ml  
PVP(C30) 0.1% w/w  
PEG 600 0.5% w/w  
ethanol 10.0% w/w

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13. Nedocromil sodium 20mg/ml  
PVP(C30) 0.1% w/w  
PEG 600 0.5% w/w  
ethanol 5.0% w/w

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14. Nedocromil sodium 20mg/ml  
PVP(C30) 0.1% w/w  
PEG 600 0.5% w/w  
ethanol 10.0% w/w

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15. Nedocromil sodium 20mg/ml  
PVP(C30) 0.05% w/w  
PEG 600 0.5% w/w  
ethanol 0.2% w/w

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16. Beclomethasone 5mg/ml  
dipropionate 0.1% w/w  
PVP/VA S-630 2.0% w/w  
ethanol

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17. Beclomethasone 5mg/ml  
dipropionate 0.1% w/w  
PVP/VA S-630 5.0% w/w  
ethanol

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18. Beclomethasone

|   |                                     |                                |
|---|-------------------------------------|--------------------------------|
| 5 | dipropionate<br>PVP(C30)<br>ethanol | 5mg/ml<br>0.1% w/w<br>5.0% w/w |
|---|-------------------------------------|--------------------------------|

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**F. Compositions containing polyvinylacetate**

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| a) in propellant 134a |                                       |                       |
|-----------------------|---------------------------------------|-----------------------|
| 1.                    | Tipredane<br>Polyvinylacetate         | 10mg/ml<br>0.042% w/w |
| 2.                    | Nedocromil sodium<br>Polyvinylacetate | 20mg/ml<br>0.042% w/w |

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| b) in propellant 227 |                                       |                       |
|----------------------|---------------------------------------|-----------------------|
| 1.                   | Tipredane<br>Polyvinylacetate         | 10mg/ml<br>0.035% w/w |
| 2.                   | Nedocromil sodium<br>Polyvinylacetate | 20mg/ml<br>0.035% w/w |

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**G. Compositions using polyvinylpyrrolidone of different K values**

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The following active ingredients were formulated in propellant 227 at the concentrations shown, with 0.1% w/w polyvinylpyrrolidone having the K value shown:

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| a) PVP(K29/32) |                          |         |
|----------------|--------------------------|---------|
| 1.             | Tipredane                | 10mg/ml |
| 2.             | Nedocromil sodium        | 20mg/ml |
| 3.             | Sodium cromoglycate      | 20mg/ml |
| 4.             | Reproterol hydrochloride | 4mg/ml  |
| 5.             | Salbutamol sulphate      | 4mg/ml  |

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| b) PVP(K90) |                   |         |
|-------------|-------------------|---------|
| 1.          | Tipredane         | 10mg/ml |
| 2.          | Nedocromil sodium | 20mg/ml |

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| c) PVP(K120) |                   |         |
|--------------|-------------------|---------|
| 1.           | Tipredane         | 10mg/ml |
| 2.           | Nedocromil sodium | 20mg/ml |

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| d) PVP(C15) |                   |         |
|-------------|-------------------|---------|
| 1.          | Tipredane         | 10mg/ml |
| 2.          | Nedocromil sodium | 20mg/ml |

30 **H. Compositions using polyvinylpyrrolidone/vinylacetate copolymers of different vinylpyrrolidone/vinylacetate ratios**

Tipredane and nedocromil sodium were formulated in propellant 227 at the concentrations shown, with 0.1% w/w PVP/VA having the vinylpyrrolidone/vinylacetate ratio shown.

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| a) Nedocromil sodium 20mg/ml |              |         |
|------------------------------|--------------|---------|
| 1.                           | PVP/VA E-535 | (50/50) |
| 2.                           | PVP/VA I-535 | (50/50) |
| 3.                           | PVP/VA E-335 | (30/70) |

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| b) Tipredane 10mg/ml |              |         |
|----------------------|--------------|---------|
| 1.                   | PVP/VA E-535 | (50/50) |
| 2.                   | PVP/VA I-535 | (50/50) |
| 3.                   | PVP/VA E-335 | (30/70) |

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## I. Further tipredane formulations

| 5  | Ex | Tipredane<br>(mg/ml) | PVP/VA S-630<br>% w/w | PVP/C30<br>% w/w | Propellant |
|----|----|----------------------|-----------------------|------------------|------------|
| 10 | 1  | 4                    | 0.0025                | -                | 134a       |
|    | 2  | 4                    | 0.01                  | -                | 134a       |
|    | 3  | 4                    | 0.025                 | -                | 134a       |
|    | 4  | 4                    | 0.05                  | -                | 134a       |
| 15 | 5  | 10                   | 0.0025                | -                | 134a       |
|    | 6  | 10                   | 0.01                  | -                | 134a       |
|    | 7  | 10                   | 0.025                 | -                | 134a       |
|    | 8  | 10                   | 0.05                  | -                | 134a       |
| 20 | 9  | 30                   | 0.0025                | -                | 134a       |
|    | 10 | 30                   | 0.01                  | -                | 134a       |
|    | 11 | 30                   | 0.025                 | -                | 134a       |
|    | 12 | 30                   | 0.05                  | -                | 134a       |
| 25 | 13 | 4                    | 0.0025                | -                | 227        |
|    | 14 | 4                    | 0.01                  | -                | 227        |
|    | 15 | 4                    | 0.025                 | -                | 227        |
|    | 16 | 4                    | 0.05                  | -                | 227        |
| 30 | 17 | 10                   | 0.0025                | -                | 227        |
|    | 18 | 10                   | 0.01                  | -                | 227        |
|    | 19 | 10                   | 0.025                 | -                | 227        |
|    | 20 | 10                   | 0.05                  | -                | 227        |
| 35 | 21 | 30                   | 0.0025                | -                | 227        |
|    | 22 | 30                   | 0.01                  | -                | 227        |
|    | 23 | 30                   | 0.025                 | -                | 227        |
|    | 24 | 30                   | 0.05                  | -                | 227        |
| 40 | 25 | 4                    | -                     | 0.0025           | 134a       |

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|    |    |    |   |        |      |
|----|----|----|---|--------|------|
| 5  | 26 | 4  | - | 0.01   | 134a |
|    | 27 | 4  | - | 0.025  | 134a |
|    | 28 | 4  | - | 0.05   | 134a |
|    | 29 | 10 | - | 0.0025 | 134a |
|    | 30 | 10 | - | 0.01   | 134a |
| 10 | 31 | 10 | - | 0.025  | 134a |
|    | 32 | 10 | - | 0.05   | 134a |
|    | 33 | 30 | - | 0.0025 | 134a |
|    | 34 | 30 | - | 0.01   | 134a |
|    | 35 | 30 | - | 0.025  | 134a |
| 15 | 36 | 30 | - | 0.05   | 134a |
|    | 37 | 4  | - | 0.0025 | 227  |
|    | 38 | 4  | - | 0.01   | 227  |
|    | 39 | 4  | - | 0.025  | 227  |
| 20 | 40 | 4  | - | 0.05   | 227  |
|    | 41 | 10 | - | 0.0025 | 227  |
|    | 42 | 10 | - | 0.01   | 227  |
|    | 43 | 10 | - | 0.025  | 227  |
| 25 | 44 | 10 | - | 0.05   | 227  |
|    | 45 | 30 | - | 0.0025 | 227  |
|    | 46 | 30 | - | 0.01   | 227  |
|    | 47 | 30 | - | 0.025  | 227  |
| 30 | 48 | 30 | - | 0.05   | 227  |

## J. Compositions containing flavouring agents

35 The following compositions were made up in propellant 227, with 0.1% w/w PVP/VA S-630.

|    |    |                   |           |
|----|----|-------------------|-----------|
| 40 | 1. | Nedocromil sodium | 20mg/ml   |
|    |    | peppermint oil    | 0.1% w/w  |
|    | 2. | Nedocromil sodium | 20mg/ml   |
|    |    | menthol           | 0.05% w/w |
|    |    | saccharin         | 0.03% w/w |
| 45 | 3. | Tipredane         | 10mg/ml   |
|    |    | menthol           | 0.05% w/w |
|    |    | saccharin         | 0.03% w/w |

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## K. Compositions containing additional excipients

The following composition was made up in propellant 227, to examine the effects of different excipients as valve lubricants.

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| a)                    |           |
|-----------------------|-----------|
| Nedocromil sodium     | 20mg/ml   |
| PVP/C30               | 0.1% w/w  |
| Lubricant             | 0.5% w/w  |
| Menthol               | 0.05% w/w |
| Saccharin, micronised | 0.03% w/w |
| Lubricants:           |           |
| PEG 200               |           |
| PEG 400               |           |
| PEG 600               |           |
| PEG 1000              |           |
| Miglyol 810           |           |
| Miglyol 829           |           |
| Miglyol 840           |           |
| Ethyl oleate          |           |
| Halocarbon oil 27     |           |
| Tyloxapol             |           |
| Polysorbate 80        |           |

| b)                    |           |
|-----------------------|-----------|
| Nedocromil sodium     | 20mg/ml   |
| PVP (C30)             | 0.10% w/w |
| PEG 1500              | 0.20% w/w |
| Menthol               | 0.05% w/w |
| Saccharin, micronised | 0.03% w/w |

| c)          |          |           |
|-------------|----------|-----------|
| Tipredane   |          | 10.0mg/ml |
| PVP (C30)   |          | 0.10% w/w |
| Lubricant   |          | 0.50% w/w |
| Lubricants: | PEG 600  |           |
|             | PEG 1000 |           |

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| d)          |                                 |           |
|-------------|---------------------------------|-----------|
| Tipredane   |                                 | 10.0mg/ml |
| PVP (C30)   |                                 | 0.10% w/w |
| Lubricant   |                                 | 0.20% w/w |
| Lubricants: | PEG 600<br>PEG 1000<br>PEG 1500 |           |

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**Claims****20 Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IE, IT, LU, MC, NL, SE, PT**

1. A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.
- 25 2. A composition according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.
3. A composition according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.
- 30 4. A composition according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.
5. A composition according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.
- 35 6. A composition according to any one of Claims 1 to 3 or Claim 5, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.
7. A composition according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.
- 40 8. A composition according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.
9. A composition according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, clemastine, acetyl- $\beta$ -methylcholine bromide and budesonide.
- 45 50 10. A process for the preparation of a composition according to Claim 1, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

**Claims for the following Contracting States : ES, GR**

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1. A process for the preparation of a pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that the polymer includes recurring structural units, the units being selected from amide containing units and

carboxylic acid ester containing units, which process comprises dispersing the powdered medicament and the polymer in the liquified hydrofluoroalkane.

2. A process according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.
- 5 3. A process according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.
4. A process according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.
- 10 5. A process according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.
6. A process according to any one of Claims 1 to 3 or Claim 5, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.
- 15 7. A process according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.
8. A process according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 20 10% w/w.
9. A process according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, 25 clemastine, acetyl- $\beta$ -methylcholine bromide and budesonide.

#### Patentansprüche

##### Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IE, IT, LU, MC, NL, SE, PT

1. Druckaerosol-Zusammensetzung mit einem verflüssigten Hydrofluoralkan, einem darin dispergierbaren, pulverförmigen Medikament und einem in dem verflüssigten Hydrofluoralkan löslichen Polymer, dadurch gekennzeichnet, daß das Polymer wiederkehrende Struktureinheiten aufweist, die unter amidhaltigen Einheiten und carbonsäure-esterhaltigen Einheiten ausgewählt sind.
- 35 2. Zusammensetzung nach Anspruch 1, wobei das Polymer wiederkehrende Struktureinheiten einschließt, die eine Amidgruppe enthalten.
3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, wobei das Polymer wiederkehrende 1-Ethylen-Pyrrolidin-2-on-Einheiten einschließt.
- 40 4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei das Polymer Polyvinylpyrrolidon ist.
5. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei das Polymer ein Copolymer ist, das wiederkehrende 1-Ethylen-Pyrrolidin-2-on-Einheiten enthält.
- 45 6. Zusammensetzung nach einem der Ansprüche 1 bis 3 oder Anspruch 5, wobei das Polymer ein Polyvinylpyrrolidon/Vinylacetat-Copolymer ist.
7. Zusammensetzung nach Anspruch 1, wobei das Polymer Polyvinylacetat oder ein Copolymer von Acrylsäure- und 50 Methacrylsäureestern ist.
8. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei die Konzentration des Polymers 0.00001 bis 10 Gew.-% beträgt.
- 55 9. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei das Medikament unter einem oder mehreren der folgenden Medikamente ausgewählt ist: Terbutalinsulfat, Beclomethasondipropionat, Salbutamolsulfat, Fluticasonpropionat, Reproterolhydrochlorid, Fenoterolhydrobromid, Natriumcromoglycat, Nedocromilnatrium, Tipredan, Pentamidinisoethionat, Clemastin, Acetyl- $\beta$ -methylcholinbromid und Budesonid.

10. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1 mit den Schritten: Dispergieren des pulverförmigen Medikaments und des Polymers in dem verflüssigten Hydrofluoralkan.

**Patentansprüche für folgende Vertragsstaaten : ES, GR**

5

1. Verfahren zur Herstellung einer Druckaerosol-Zusammensetzung mit einem verflüssigten Hydrofluoralkan, einem darin dispergierbaren, pulverförmigen Medikament und einem in dem verflüssigten Hydrofluoralkan löslichen Polymer, dadurch gekennzeichnet, daß das Polymer wiederkehrende Struktureinheiten aufweist, die unter amidhaltigen Einheiten und carbonsäureesterhaltigen Einheiten ausgewählt sind, mit den Verfahrensschritten: Dispergieren des pulverförmigen Medikaments und des Polymers in dem verflüssigten Hydrofluoralkan.

10

2. Verfahren nach Anspruch 1, wobei das Polymer wiederkehrende Struktureinheiten einschließt, die eine Amidgruppe enthalten.

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3. Verfahren nach Anspruch 1 oder Anspruch 2, wobei das Polymer wiederkehrende 1-Ethylen-Pyrrolidin-2-on-Einheiten einschließt.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Polymer Polyvinylpyrrolidon ist.

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5. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Polymer ein Copolymer ist, das wiederkehrende 1-Ethylen-Pyrrolidin-2-on-Einheiten enthält.

6. Verfahren nach einem der Ansprüche 1 bis 3 oder Anspruch 5, wobei das Polymer ein Polyvinylpyrrolidon/Vinylacetat-Copolymer ist.

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7. Verfahren nach Anspruch 1, wobei das Polymer Polyvinylacetat oder ein Copolymer von Acrylsäure- und Methacrylsäureestern ist.

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8. Verfahren nach einem der vorhergehenden Ansprüche, wobei die Konzentration des Polymers 0.00001 bis 10 Gew.-% beträgt.

35

9. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Medikament unter einem oder mehreren der folgenden Medikamente ausgewählt ist: Terbutalinsulfat, Beclomethasondipropionat, Salbutamolsulfat, Fluticason-propionat, Reoproterolhydrochlorid, Fenoterolhydrobromid, Natriumcromoglycat, Nedocromilnatrium, Tipredan, Pentamidinisoethionat, Clemastin, Acetyl-β-methylcholinbromid und Budesonid.

**Revendications**

**Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IE, IT LU, MC, NL, SE, PT**

40

1. Composition aérosol sous pression comprenant un hydrofluoroalcane liquéfié, un médicament en poudre pouvant s'y disperser et une matière polymère soluble dans l'hydrofluoroalcane liquéfié, caractérisé en ce que la matière polymère comprend des unités structurales récurrentes, les unités étant choisies parmi les unités contenant une ami de et les unités contenant un ester d'acide carboxylique.

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2. Composition selon la Revendication 1, dans laquelle la matière polymère comprend des unités structurales récurrentes contenant un groupe amide.

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3. Composition selon la Revendication 1 ou la Revendication 2, dans laquelle la matière polymère comprend des unités 1-éthylène-pyrrolidin-2-one récurrentes.

4. Composition selon l'une quelconque des Revendications 1 à 3, dans laquelle la matière polymère est la polyvinylpyrrolidone.

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5. Composition selon l'une quelconque des Revendications 1 à 3, dans laquelle la matière polymère est un copolymère contenant des unités 1-éthylène-pyrrolidin-2-one récurrentes.

6. Composition selon l'une quelconque des Revendications 1 à 3 ou selon la Revendication 5, dans laquelle la matière polymère est un copolymère de polyvinylpyrrolidone et d'acétate de vinyle.

7. Composition selon la Revendication 1, dans laquelle la matière polymère est l'acétate de polyvinyle ou un copolymère de l'acide acrylique et d'esters de l'acide méthacrylique.
8. Composition selon l'une quelconque des Revendications précédentes dans laquelle la concentration en matière polymère est comprise entre 0.00001 et 10% en poids.
9. Composition selon l'une quelconque des Revendications précédentes, dans laquelle le médicament est choisi parmi un ou plusieurs des composés sulfate de terbutaline, dipropionate de bêclométhasone, sulfate de salbutamol, propionate de fluticasone, chlorhydrate de réprotérol, bromhydrate de fénotérol, cromoglycate de sodium, nedocromil sodique, tiprédane, isoéthionate de pentamidine, clémastine, bromure d'acétyl-β-méthylcholine et budésonide.
10. Procédé pour la préparation d'une composition selon la Revendication 1, qui comprend la dispersion du médicament en poudre et de la matière polymère dans l'hydrofluoroalcane liquéfié.

15 Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'une composition aérosol sous pression qui comprend un hydrofluoroalcane liquéfié, un médicament en poudre pouvant s'y disperser et une matière polymère soluble dans l'hydrofluoroalcane liquéfié, caractérisé en ce que la matière polymère comprend des unités structurales récurrentes, les unités étant choisies parmi les unités contenant une amide et les unités contenant un ester d'acide carboxylique, lequel procédé comprend la dispersion du médicament en poudre et de la matière polymère dans l'hydrofluoroalcane liquéfié.
2. Procédé selon la Revendication 1, dans lequel la matière polymère comprend des unités structurales récurrentes contenant un groupe amide.
- 25 3. Procédé selon la Revendication 1 ou la Revendication 2, dans lequel la matière polymère comprend des unités 1-éthylène-pyrrolidin-2-one récurrentes.
4. Procédé selon l'une quelconque des Revendications 1 à 3, dans lequel la matière polymère est la polyvinylpyrrolidone.
- 30 5. Procédé selon l'une quelconque des Revendications 1 à 3, dans lequel la matière polymère est un copolymère contenant des unités 1-éthylène-pyrrolidin-2-one récurrentes.
- 35 6. Procédé selon l'une quelconque des Revendications 1 à 3 ou selon la Revendication 5, dans lequel la matière polymère est un copolymère de polyvinylpyrrolidone et d'acétate de vinyle.
7. Procédé selon la Revendication 1, dans lequel la matière polymère est de l'acétate de polyvinyle ou un copolymère d'acide acrylique et d'esters de l'acide méthacrylique.
- 40 8. Procédé selon l'une quelconque des Revendications précédentes, dans lequel la concentration en matière polymère est comprise entre 0,00001 et 10% en poids.
9. Procédé selon l'une quelconque des Revendications précédentes, dans lequel le médicament est choisi parmi un ou plusieurs des composés sulfate de terbutaline, dipropionate de bêclométhasone, sulfate de salbutamol, propionate de fluticasone, chlorhydrate de réprotérol, bromhydrate de fénotérol, cromoglycate de sodium, nedocromil sodique, tiprédane, isoéthionate de pentamidine, clémastine, bromure d'acétyl-β-méthylcholine et budésonide.

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(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 605 578 B2

(12)

## NEW EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the opposition decision:  
22.09.1999 Bulletin 1999/38

(51) Int. Cl. 6: A61K 9/00, A61K 9/12

(45) Mention of the grant of the patent:  
10.01.1996 Bulletin 1996/02

(86) International application number:  
PCT/GB92/01749

(21) Application number: 92920611.8

(87) International publication number:  
WO 93/05765 (01.04.1993 Gazette 1993/09)

(22) Date of filing: 23.09.1992

### (54) PRESSURISED AEROSOL COMPOSITIONS

UNTER DRUCK AEROSOLZUSAMMENSETZUNGEN  
COMPOSITIONS POUR AEROSOLS SOUS PRESSION

(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL  
PT SE

(74) Representative: Caffin, Lee et al  
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(30) Priority: 25.09.1991 GB 9120396  
28.09.1991 GB 9120675  
19.11.1991 GB 9124661  
14.02.1992 GB 9203212

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WO-A-87/05210 WO-A-87/05211  
WO-A-91/11173 US-A- 4 025 635  
US-A- 4 752 466

(43) Date of publication of application:  
13.07.1994 Bulletin 1994/28

- Statement of Julie-Ann Wyber
- Statement of Alexander Bell
- Statement of Dr. John J. Schiarra
- Part of the transcript of Dr Schiarra's evidence

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#### Remarks:

Consolidated with 92308657.3/0534731 (European  
application No./publication No.) by decision dated  
12.10.94.

EP 0 605 578 B2

## Description

[0001] This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

5 [0002] Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquefied chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste-and odour-free.

10 [0003] In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all application of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

15 [0004] The use of hydrofluorocarbons as aerosol propellants has also been suggested. However, considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofluoroalkanes and capable of stabilising medicaments suspensions.

[0005] Surprisingly, we have found that certain polymers are both soluble in the aerosol propellants and capable of stabilising medicament compositions.

20 [0006] Thus, according to the invention, we provide a pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that said polymer is selected from the group consisting of polymers including recurring amide containing structural units, polyvinylacetate and acrylic acid/methacrylic acid ester copolymers.

[0007] The polymer may be a homopolymer, that is the polymer consists of the same recurring structural units, or it

25 may be a copolymer, that is the polymer contains recurring units in addition to amide containing units. acid ester The polymer may also be a copolymer of amide containing units and carboxylic acid ester units. Such copolymers may be either block copolymers or random copolymers.

[0008] We prefer polymers which include recurring structural units containing an amide group. We particularly prefer the amide containing unit to be 1-ethylene-pyrrolidin-2-one. We especially prefer the polymer to be a homopolymer containing recurring 1-ethylene-pyrrolidin-2-one, that is polyvinylpyrrolidone.

30 [0009] In general, we have found that polyvinylpyrrolidones having a wide range of average molecular weights give acceptable suspensions. Although polymers can be characterised by their weight average molecular weights, viscosity average molecular weights or number average molecular weights, it is more usual to characterise polymers, in particular polymers such as polyvinylpyrrolidone, by K values, in which K is determined from viscosity measurements using

35 the Fikentscher equation (H. Fikentscher, *Cellulosechemie*, 1932, 13, 58-64 and 71-74). In particular we prefer the polymer to have a K value of from 10 to 150, more preferably 15 to 120. Particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125.

[0010] Suitable polymers containing carboxylic acid ester containing recurring structural units include polyvinylacetate and copolymers of vinyl acetate and vinyl pyrrolidone, that is polyvinylpyrrolidone/vinyl acetate copolymer. We have

40 found that polyvinylacetate with a weight average molecular weight of 250,000 gives particularly stable suspensions.

[0011] Other polymers that may be mentioned include acrylic acid/methacrylic acid ester copolymers, especially those in which the methyl and ethyl ester groups have been replaced with a low content of trimethylammoniummethyl groups, preferably at a ratio of 1:20, especially at a ratio of 1:40. We have found that such copolymers having a weight average molecular weight of 150,000 give stable suspensions.

45 [0012] The amount of polymer in the composition will depend on the active ingredient to be dispersed, its concentration and the particular polymer selected. However, in general the amount of polymer is from 0.00001 to 10% w/w, more preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w.

[0013] The compositions may, in addition to the polymer, contain other excipients, in particular excipients intended to improve valve lubrication and excipients to modify flavour. Particular lubricants that may be mentioned include polyethoxylated compounds, especially polyethylene glycol. We prefer polyethylene glycol having a mean molecular weight of from 200 to 3000, preferably 400 to 2000, eg 1500. Other polyethoxylated compounds that may be used as lubricants include polysorbates, eg polysorbate 80, and alkyl aryl polyether alcohols, eg tyloxapol. Other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofluorocarbons and esters of medium chain fatty acids. The amount of lubricant in the composition will depend on the other components of the composition, the active ingredient, the nature of the valve, etc. In general, we prefer a concentration of 0.01 to 4% w/w and more preferably 0.1 to 2% w/w.

[0014] Flavour modifying excipients that may be added to the composition include peppermint oil, menthol, Dentomint (Dentomint is a tradename), saccharin and saccharin sodium. When the flavour modifying excipient is a solid, preferably

it is micronised. The concentration will depend on the individual composition and the flavour modifying excipient. In general, we prefer a concentration of 0.005 to 4% w/w; more preferably 0.01 to 1% w/w.

[0015] By the term 'hydrofluoroalkane' we mean a compound of general formula

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in which x is an integer from 1 to 3, y+z=2x+2 and y and z are both at least 1.

[0016] Particular hydrofluoroalkanes of interest are  $CF_3CFH_2$  (Propellant 134a),  $CH_3CHF_2$  (Propellant 152a) and  $CF_3CHFCF_3$  (Propellant 227). We particularly prefer compositions including propellant 227.

10 [0017] In general the vapour pressure of the propellant mixture should be in the range suitable and permitted for aerosol propellants. The vapour pressure may be varied by mixing one or more hydrofluoroalkanes and/or some other suitable vapour pressure modifying agent in appropriate proportions.

[0018] We prefer the vapour pressure of the mixture to be in the range 20 to 100 psig, more preferably 40 to 80 psig, eg about 60 psig.

15 [0019] In certain cases we have found it advantageous to add to the compositions excipients capable of increasing the solubility of the polymer or of other excipients, in the propellant. In general we have found that the polymers selected have a solubility in the propellant of at least 0.0001% w/w, preferably at least 0.001% w/w, particularly 0.01% w/w and especially 0.1% w/w. Excipients capable of increasing the solubility of the polymer include liquid excipients which are more polar than the liquefied propellant, where polarity is defined in terms of relative Kauri butanol values, as described 20 in European patent application 0 372 777. Particular excipients that may be mentioned include alcohols eg ethanol and isopropanol. However, in contrast to the teaching of EP 0 372 777, we have found that only very small quantities of such excipients are required. In particular we have found that good compositions can be prepared in propellant 134a with polyvinylpyrrolidone as polymer with a variety of active ingredients and less than 10% w/w, preferably less than 5% w/w, more preferably less than 2% w/w, eg 0.2% w/w ethanol.

25 [0020] Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments which are conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone propionate, budesonide and ipratropium bromide, ortiptopium bromide and atropine and combinations of two or more of these agents, eg a combination of a prophylactic agent with a bronchodilator, eg sodium cromoglycate with salbutamol.

30 [0021] Other medicaments that may be mentioned include antihistamines, eg clemastine, pentamidine and salts thereof, acetyl- $\beta$ -methylcholine bromide, peptide hormones such as insulin and amylin, bradykinin antagonists, PLA<sub>2</sub> inhibitors, PAF antagonists, lipoxygenase inhibitors, leukotriene antagonists, CNS active drugs, such as NMDA antagonists, glutamate antagonists, CCK agonists and antagonists; macrolide compounds including FK 506, rapamycin, cyclosporin and structurally related compounds, vitamins, vaccines, eg MMR vaccine and polio vaccine and vectors for gene therapy, eg plasmids containing genes intended to correct genetic disorders such as cystic fibrosis.

35 [0022] Where the medicament is intended for delivery to the lung, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the medicament is preferably in a form having a mass median diameter of from 0.01 to 10  $\mu$ m, more preferably from 0.1 to 4  $\mu$ m, eg about 2 or 3  $\mu$ m.

40 [0023] The amount of medicament in the composition will depend on the nature of the active ingredient and the condition to be treated. However, the composition preferably comprises from 0.01 to 15% w/w, preferably from 0.1 to 10% w/w, and most preferably from 0.5 to 5% w/w medicament.

45 [0024] According to a further aspect of the invention there is provided a method of producing a pressurised aerosol composition as herein described, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

50 [0025] In particular, the compositions may be produced by cold fill or pressure fill techniques. In cold filling, the ingredients are placed in a cooled mixing vessel, cooled liquefied propellant added and a dispersion produced by vigorous stirring. Alternatively, a slurry may be prepared of the ingredients in a portion of cooled liquid propellant and the remainder of the liquefied propellant added under vigorous stirring. Aliquots of the dispersed composition are then filled into cooled aerosol cans and sealed with a suitable valve, eg a metering valve.

55 [0026] In pressure filling, the ingredients are placed in a pressure vessel, liquefied propellant added under pressure through a valve and a dispersion of the ingredients in the liquefied dispersed composition are then filled, under pressure, through the valve into suitable cans provided with appropriate valves, eg metering valves.

[0027] The compositions according to the invention are advantageous in that the solubility of the polymer is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve.

[0028] The compositions of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

[0029] The performance of the compositions according to the present invention can be assessed using the following test procedures:

**1. Settling times**

[0030] A glass bottle containing the composition is gently shaken five times and then stood upright. The time interval between standing the bottle upright and the first appearance of flocculation or separation of powder in the propellant determined ( $S_1$ ). Timing is continued until complete separation, defined as when three lines of standard newspaper print can be read through the propellant from the top or bottom, depending on whether the active ingredient floats or sinks ( $S_2$ ). In some compositions, complete separation does not occur. For these compositions, a turbidity factor ranging from 1 to 5 is determined, 1 denoting that a small proportion of the active ingredient is suspended and 5 denoting that the majority of the active ingredient is suspended.

**2. Dispersion Tests**

[0031] Dispersion testing on compositions formulated in cans having a metering valve can be assessed using a glass multistage liquid impinger, eg of the type described by J.H. Bell *et al*, *J. Pharm. Sci.*, 1971, **60**(10), 1559.

**3. Lubrication**

[0032] The lubricating effects of the composition can be assessed by filling the formulation into a can and closing the can with a modified metering valve from which the return spring has been removed. The stem of the valve is subjected to a compression force and the reading recorded in Newtons. This gives a measure of the lubricating efficacy of the composition.

**4. Dose uniformity**

[0033] Dose uniformity is assessed by discharging a metered dose aerosol can containing the composition into a filter tube which has sufficient air flowing through it to entrain all the dose. The tube is washed out with a suitable solvent and the amount of medicament assayed. The medicament entrained on the mouthpiece is also washed off and assayed. The variation of dose evaluated throughout the life of the can is a measure of dose uniformity. In a variation of this test, dose uniformity after standing can be assessed by shaking the aerosol can, allowing to stand for a predetermined time and assessing dose in the manner described above.

**40 5. Caking potential**

[0034] Compositions to be assessed are filled into plastic coated glass bottles. The assessment is carried out by allowing the samples to be stored for a period of time in order that complete sedimentation and compaction of the powder mass can take place, eg 3 months. After that period, the glass bottles are shaken by gentle twisting of the hand to totally invert the bottles. The number of bottle inversions required to completely resuspend the drug is noted. The number gives a measure of the degree of compaction of the composition. Since ease of drug particle redispersion is essential for dose uniformity, any composition requiring more than 5 shakes suggests possible problems in long-term storage.

[0035] The invention will now be illustrated, but in no way limited, by the following Examples.

**50 Examples**

**Method**

[0036] The required amounts of micronised active ingredient, suspending agent and other excipients, were weighed into plastic coated glass bottles and crimped with an appropriate valve. The desired amount of liquefied propellant was then transferred using a transfer button and the contents of the bottle sonicated to ensure thorough mixing. Unless otherwise stated, the fill volume for the bottles was 20 ml.

**Materials****Active ingredients**

5 [0037] All active ingredients were micronised. In general, the active ingredients were anhydrous, although nedocromil sodium and sodium cromoglycate were used in their equilibrium hydrated form which each contain about 10% w/w water at room temperature.

**Polyethyleneglycols (PEG)**

10 [0038] The average molecular weight of the polyethyleneglycol used is indicated by the number 200, 400, etc following PEG.

**Halocarbon oil**

15 [0039] Halocarbon oil is the proprietary name given to a series of high molecular weight fully halogenated chlorofluorocarbons of chlorotrifluoroethylene telomers obtainable from Halocarbon Products Corporation, New Jersey, USA.

**Miglyols**

20 **Miglyol® neutral oils**

[0040] Miglyol® neutral oils are esters of medium chain fatty acids and are sometimes referred to as fractionated coconut oils. Miglyol is a trademark of Hüls AG. The following oils were used.

25 **Miglyol® 810**

[0041] A triglyceride of fractionated C<sub>8</sub>/C<sub>10</sub> coconut oil fatty acids classified by the CTFA as caprylic/capric triglyceride. It meets the requirements of the British Pharmacopoeia 1988 for the monograph "Fractionated Coconut Oil". It is a low viscosity oil of neutral taste and smell, with a turbidity point below 0°C.

**Miglyol® 829**

35 [0042] A glyceryl ester of fractionated C<sub>8</sub>/C<sub>10</sub> coconut fatty acids linked to succinic acid and is classified by the CTFA as caprylic/capric/diglyceryl succinate. It has a turbidity point below -30°C, is soluble in alcohol, has a viscosity of approximately 250 mPa.s and a density of approximately 1.

**Miglyol® 840**

40 [0043] A propylene glycol diester of saturated vegetable fatty acids with C<sub>8</sub>/C<sub>10</sub> chain lengths, classified by the CFTA as propyleneglycol dicaprylate/dicaprate. It meets the requirements of the German Pharmacopoeia, DAR9, 1st supplement, for the monograph "Propyleneglycoloctanoatodecanoate". It has a turbidity point below -30°C and is soluble in 90% ethanol.

45 **Polyvinylpyrrolidones**

[0044] All polyvinylpyrrolidones used were essentially linear homopolymers formed by the free radical polymerisation of N-vinylpyrrolidone. PVP(K29/32), PVP(K90), PVP(K120), PVP(C15) and PVP(C30) refer to the polyvinylpyrrolidones obtainable from GAF Chemical Corporation and sold under the Trade Mark PLASDONE®. PVP/17PF refers to KOL-LIDON 17PF, a polyvinylpyrrolidone available from BASF (KOLLIDON is a registered Trade Mark).

50 [0045] The manufacturing processes for polyvinylpyrrolidone and the other polymers used herein produce polymer mixtures containing molecules of unequal chain length and thus different molecular weights. Such polymers are usually characterised by their K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellulosechemie*, 1932, 13, 58-64 and 71-74). The polymers can also be characterised by their average molecular weights (M<sub>w</sub>), viscosity average molecular weights (M<sub>v</sub>) and number average molecular weights (M<sub>n</sub>).

[0046] Characterising data for the polyvinylpyrrolidones used were as follows:

|    | K         | M <sub>w</sub> | M <sub>v</sub> | M <sub>n</sub> |
|----|-----------|----------------|----------------|----------------|
| 5  | PVP 17 PF | 15-18          | 9000           | -              |
|    | K29/32    | 29-32          | -              | -              |
| 10 | K90       | 94±6           | 1,280,000      | 63000          |
|    | K120      | 120±5          | 2,800,000      | 1,450,000      |
|    | C15       | 17±1           | 10500          | 7000           |
|    | C30       | 30.5±1         | 62500          | 3800           |
|    |           |                |                | 16500          |

15 **Polyvinylpyrrolidone/vinylacetate copolymers**

[0047] Polyvinylpyrrolidone/vinylacetate copolymers are obtainable from GAF Chemical Corporation. The E- and I-series of PVP/VA copolymers were supplied as 50% solutions in ethanol and isopropanol respectively. S-630 refers to the white, spray dried polymer of PVP/VA having the characteristics set out below. Characterising data for PVP/VA used:

|    |        | K value | VP/VA ratio |
|----|--------|---------|-------------|
| 25 | PVP/VA | S-630   | 30-50       |
|    |        | E-535   | 30-50       |
| 30 |        | I-535   | 25-35       |
|    |        | E-335   | 25-35       |
|    |        |         | 30/70       |

35 **Acrylic acid/methacrylic acid ester copolymers**

[0048] The acrylic acid/methacrylic acid ester copolymers used were copolymers synthesized from acrylic and methacrylic acid ethyl and methyl esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the neutral (meth)acrylic acid esters is 1:40. The weight average molecular weight is approximately 150000. The polymer used was EUDRAGIT RS PM, obtainable from Röhm Pharma GmbH. (EUDRAGIT is a registered 40 Trade Mark).

**Polyvinylacetate**

[0049] The polyvinylacetate used had a weight average molecular weight of about 26,000.

45 **A. Compositions containing polyvinylpyrrolidone and propellant 227**

[0050] The following active ingredients were formulated at the concentration shown with PVP in propellant 227 PLAS-DONE C30 (PLASDONE is a registered Trade Mark of GAF Chemicals Corporation).

| a) with 0.05% w/w PVP(C-30) |    |                             |        |
|-----------------------------|----|-----------------------------|--------|
| 55                          | 1. | Terbutaline sulphate        | 5mg/ml |
|                             | 2. | Beclomethasone dipropionate | 5mg/ml |
|                             | 3. | Salbutamol sulphate         | 4mg/ml |

(continued)

| a) with 0.05% w/w PVP(C-30) |  |          |
|-----------------------------|--|----------|
| 5                           | 4. Fluticasone propionate                  | 4mg/ml   |
|                             | 5. Reproterol hydrochloride                | 10mg/ml  |
|                             | 6. Fenoterol hydrobromide                  | 4mg/ml   |
|                             | 7. Sodium cromoglycate                     | 10mg/ml  |
| 10                          | 8. Sodium cromoglycate                     | 50mg/ml  |
|                             | 9. Ipratropium bromide                     | 0.8mg/ml |
|                             | 10. Pentamidine isoethionate               | 4mg/ml   |
|                             | 11. Clemastine                             | 4mg/ml   |
| 15                          | 12. Acetyl- $\beta$ -methylcholine bromide | 10mg/ml  |
|                             | 13. Budesonide                             | 4mg/ml   |

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| b) with 0.1% w/v PVP(17PF) |                           |        |
|----------------------------|---------------------------|--------|
| 25                         | 1. Fenoterol hydrobromide | 4mg/ml |
|                            | 2. Terbutaline sulphate   | 5mg/ml |
|                            | 3. Salbutamol sulphate    | 4mg/ml |

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| c) with 0.025% w/v PVP(C30) |              |         |
|-----------------------------|--------------|---------|
| 35                          | 1. Tipredane | 10mg/ml |

**B. Compositions containing polyvinylpyrrolidone/vinyl acetate copolymer in propellant 227**

40 [0051] The following active ingredients were formulated in propellant 227 at the concentrations shown.

| a) with 0.05% w/v PVP/VA S-630 |                                |          |
|--------------------------------|--------------------------------|----------|
| 45                             | 1. Terbutaline sulphate        | 5mg/ml   |
|                                | 2. Beclomethasone dipropionate | 5mg/ml   |
|                                | 3. Salbutamol sulphate         | 4mg/ml   |
| 50                             | 4. Fluticasone propionate      | 4mg/ml   |
|                                | 5. Reproterol hydrochloride    | 10mg/ml  |
|                                | 6. Fenoterol hydrobromide      | 4mg/ml   |
|                                | 7. Sodium cromoglycate         | 10mg/ml  |
| 55                             | 8. Sodium cromoglycate         | 50mg/ml  |
|                                | 9. Ipratropium bromide         | 0.8mg/ml |

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(continued)

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| a) with 0.05% w/v PVP/VA S-630 |  |         |
|--------------------------------|--|---------|
| 10.                            | Acetyl- $\beta$ -methylcholine bromide | 10mg/ml |
| 11.                            | Budesonide                             | 4mg/ml  |

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**C. Compositions containing PVP or PVP/VA, propellant 227 and polyethylene glycol**

[0052] The following active ingredients were formulated in propellant 227 at the concentration shown with 0.5% w/v PEG600.

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| a) with 0.05% w/v PVP(C30) |                          |         |
|----------------------------|--------------------------|---------|
| 1.                         | Salbutamol sulphate      | 4mg/ml  |
| 2.                         | Sodium cromoglycate      | 50mg/ml |
| 3.                         | Reprotoxol hydrochloride | 10mg/ml |

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| b) with 0.05% w/v PVP/VA S-630 |                          |         |
|--------------------------------|--------------------------|---------|
| 1.                             | Salbutamol sulphate      | 4mg/ml  |
| 2.                             | Sodium cromoglycate      | 50mg/ml |
| 3.                             | Reprotoxol hydrochloride | 10mg/ml |
| 4.                             | Budesonide               | 4mg/ml  |

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| c) with 0.1% w/v PVP(17PF) |                        |        |
|----------------------------|------------------------|--------|
| 1.                         | Terbutaline sulphate   | 5mg/ml |
| 2.                         | Fenoterol hydrobromide | 4mg/ml |

**D. Compositions containing acrylic acid/methacrylic acid ester copolymers and propellant 227**

55 [0053] The following active ingredients were formulated at the concentration shown with 0.1% w/v EUDRAGIT RS (EUDRAGIT is a Trade Mark of Röhm Pharma GmbH) in propellant 227.

5

| a)  |  |          |
|-----|--|----------|
| 1.  | Terbutaline                            | 5mg/ml   |
| 2.  | Beclomethasone dipropionate            | 5mg/ml   |
| 3.  | Salbutamol sulphate                    | 4mg/ml   |
| 4.  | Fluticasone                            | 4mg/ml   |
| 5.  | Reproterol hydrochloride               | 10mg/ml  |
| 6.  | Fenoterol                              | 4mg/ml   |
| 7.  | Sodium cromoglycate                    | 10mg/ml  |
| 8.  | Ipratropium bromide                    | 0.8mg/ml |
| 9.  | Clemastine                             | 4mg/ml   |
| 10. | Acetyl- $\beta$ -methylcholine bromide | 10mg/ml  |

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| b) compositions including 0.5%w/w PEG 600 |                             |         |
|---|-----------------------------|---------|
| 11.                                       | Beclomethasone dipropionate | 5mg/ml  |
| 12.                                       | Sodium cromoglycate         | 50mg/ml |
| 13.                                       | Reproterol hydrochloride    | 10mg/ml |
| 14.                                       | Fenoterol hydrobromide      | 4mg/ml  |

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#### E. Compositions in propellant 134a

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[0054] The following active ingredients were formulated at the concentration shown in propellant 134a.

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|    |    |  |                                  |
|----|----|--|----------------------------------|
| 5  | 1. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 10 | 2. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.1% w/w<br>10.0% w/w |
| 15 | 3. | Nedocromil sodium<br>PVP(C30)<br>ethanol | 20mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 20 | 4. | Nedocromil sodium<br>PVP(C30)<br>ethanol | 20mg/ml<br>0.1% w/w<br>10.0% w/w |
| 25 | 5. | Tipredane<br>PVP/VA S-630<br>ethanol     | 10mg/ml<br>0.1% w/w<br>5.0% w/w  |
| 30 | 6. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.25% w/w<br>5.0% w/w |
| 35 | 7. | Tipredane<br>PVP(C30)<br>ethanol         | 10mg/ml<br>0.5% w/w<br>5.0% w/w  |

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|    |     |   |  |
|----|-----|---|--|
| 5  | 8.  | Nedocromil sodium<br>PVP/VA S-630<br>ethanol              | 20mg/ml<br>0.1% w/w<br>5.0% w/w              |
| 10 | 9.  | Nedocromil sodium<br>PVP/C30<br>ethanol                   | 20mg/ml<br>0.25% w/w<br>5.0% w/w             |
| 15 | 10. | Nedocromil sodium<br>PVP(C30)<br>ethanol                  | 20mg/ml<br>0.5% w/w<br>5.0% w/w              |
| 20 | 11. | Tipredane<br>PVP(C30)<br>PEG 600<br>ethanol               | 10mg/ml<br>0.1% w/w<br>0.5% w/w<br>5.0% w/w  |
| 25 | 12. | Tipredane<br>PVP(C30)<br>PEG 600<br>ethanol               | 10mg/ml<br>0.1% w/w<br>0.5% w/w<br>10.0% w/w |
| 30 | 13. | Nedocromil sodium<br>PVP(C30)<br>PEG 600<br>ethanol       | 20mg/ml<br>0.1% w/w<br>0.5% w/w<br>5.0% w/w  |
| 35 | 14. | Nedocromil sodium<br>PVP(C30)<br>PEG 600<br>ethanol       | 20mg/ml<br>0.1% w/w<br>0.5% w/w<br>10.0% w/w |
| 40 | 15. | Nedocromil sodium<br>PVP(C30)<br>PEG 600<br>ethanol       | 20mg/ml<br>0.05% w/w<br>0.5% w/w<br>0.2% w/w |
| 45 | 16. | Beclomethasone<br>dipropionate<br>PVP/VA S-630<br>ethanol | 5mg/ml<br>0.1% w/w<br>2.0% w/w               |
| 50 | 17. | Beclomethasone<br>dipropionate<br>PVP/VA S-630<br>ethanol | 5mg/ml<br>0.1% w/w<br>5.0% w/w               |
| 55 | 18. | Beclomethasone  |  |

|   |                                     |                                |
|---|-------------------------------------|--------------------------------|
| 5 | dipropionate<br>PVP(C30)<br>ethanol | 5mg/ml<br>0.1% w/w<br>5.0% w/w |
|---|-------------------------------------|--------------------------------|

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**F. Compositions containing polyvinylacetate**

[0055]

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| a) in propellant 134a |                   |         |            |
|-----------------------|-------------------|---------|------------|
| 1.                    | Tipredane         | 10mg/ml |            |
| 2.                    | Polyvinylacetate  |         | 0.042% w/w |
|                       | Nedocromil sodium | 20mg/ml |            |
|                       | Polyvinylacetate  |         | 0.042% w/w |

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| b) in propellant 227 |                   |         |            |
|----------------------|-------------------|---------|------------|
| 1.                   | Tipredane         | 10mg/ml |            |
| 2.                   | Polyvinylacetate  |         | 0.035% w/w |
|                      | Nedocromil sodium | 20mg/ml |            |
|                      | Polyvinylacetate  |         | 0.035% w/w |

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**G. Compositions using polyvinylpyrrolidone of different K values**  
 [0056] The following active ingredients were formulated in propellant 227 at the concentrations shown, with 0.1% w/w polyvinylpyrrolidone having the K value shown:

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| a) PVP(K29/32) |                          |         |  |
|----------------|--------------------------|---------|--|
| 1.             | Tipredane                | 10mg/ml |  |
| 2.             | Nedocromil sodium        | 20mg/ml |  |
| 3.             | Sodium cromoglycate      | 20mg/ml |  |
| 4.             | Reprotohol hydrochloride | 4mg/ml  |  |
| 5.             | Salbutamol sulphate      | 4mg/ml  |  |

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| b) PVP(K90) |                   |         |
|-------------|-------------------|---------|
| 1.          | Tipredane         | 10mg/ml |
| 2.          | Nedocromil sodium | 20mg/ml |

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| c) PVP(K120) |                   |         |
|--------------|-------------------|---------|
| 1.           | Tipredane         | 10mg/ml |
| 2.           | Nedocromil sodium | 20mg/ml |

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| d) PVP(C15) |                   |         |
|-------------|-------------------|---------|
| 1.          | Tipredane         | 10mg/ml |
| 2.          | Nedocromil sodium | 20mg/ml |

30 **H. Compositions using polyvinylpyrrolidone/vinylacetate copolymers of different vinylpyrrolidone/vinylacetate ratios**

[0057] Tipredane and nedocromil sodium were formulated in propellant 227 at the concentrations shown, with 0.1% w/w PVP/VA having the vinylpyrrolidone/vinylacetate ratio shown.

35

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| a) Nedocromil sodium 20mg/ml |              |         |
|------------------------------|--------------|---------|
| 1.                           | PVP/VA E-535 | (50/50) |
| 2.                           | PVP/VA I-535 | (50/50) |
| 3.                           | PVP/VA E-335 | (30/70) |

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| b) Tipredane 10mg/ml |              |         |
|----------------------|--------------|---------|
| 1.                   | PVP/VA E-535 | (50/50) |
| 2.                   | PVP/VA I-535 | (50/50) |
| 3.                   | PVP/VA E-335 | (30/70) |

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## I. Further tipredane formulations

[0058]

| 5  | Ex | Tipredane<br>(mg/ml) | PVP/VA S-630<br>% w/w | PVP/C30<br>% w/w | Propellant |
|----|----|----------------------|-----------------------|------------------|------------|
| 10 | 1  | 4                    | 0.0025                | -                | 134a       |
|    | 2  | 4                    | 0.01                  | -                | 134a       |
|    | 3  | 4                    | 0.025                 | -                | 134a       |
|    | 4  | 4                    | 0.05                  | -                | 134a       |
|    | 5  | 10                   | 0.0025                | -                | 134a       |
| 15 | 6  | 10                   | 0.01                  | -                | 134a       |
|    | 7  | 10                   | 0.025                 | -                | 134a       |
|    | 8  | 10                   | 0.05                  | -                | 134a       |
|    | 9  | 30                   | 0.0025                | -                | 134a       |
|    | 10 | 30                   | 0.01                  | -                | 134a       |
| 20 | 11 | 30                   | 0.025                 | -                | 134a       |
|    | 12 | 30                   | 0.05                  | -                | 134a       |
|    | 13 | 4                    | 0.0025                | -                | 227        |
|    | 14 | 4                    | 0.01                  | -                | 227        |
|    | 15 | 4                    | 0.025                 | -                | 227        |
| 25 | 16 | 4                    | 0.05                  | -                | 227        |
|    | 17 | 10                   | 0.0025                | -                | 227        |
|    | 18 | 10                   | 0.01                  | -                | 227        |
|    | 19 | 10                   | 0.025                 | -                | 227        |
|    | 20 | 10                   | 0.05                  | -                | 227        |
| 30 | 21 | 30                   | 0.0025                | -                | 227        |
|    | 22 | 30                   | 0.01                  | -                | 227        |
|    | 23 | 30                   | 0.025                 | -                | 227        |
|    | 24 | 30                   | 0.05                  | -                | 227        |
|    | 25 | 4                    | -                     | 0.0025           | 134a       |

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|    |    |   |        |      |
|----|----|---|--------|------|
| 26 | 4  | - | 0.01   | 134a |
| 27 | 4  | - | 0.025  | 134a |
| 28 | 4  | - | 0.05   | 134a |
| 29 | 10 | - | 0.0025 | 134a |
| 30 | 10 | - | 0.01   | 134a |
| 31 | 10 | - | 0.025  | 134a |
| 32 | 10 | - | 0.05   | 134a |
| 33 | 30 | - | 0.0025 | 134a |
| 34 | 30 | - | 0.01   | 134a |
| 35 | 30 | - | 0.025  | 134a |
| 36 | 30 | - | 0.05   | 134a |
| 37 | 4  | - | 0.0025 | 227  |
| 38 | 4  | - | 0.01   | 227  |
| 39 | 4  | - | 0.025  | 227  |
| 40 | 4  | - | 0.05   | 227  |
| 41 | 10 | - | 0.0025 | 227  |
| 42 | 10 | - | 0.01   | 227  |
| 43 | 10 | - | 0.025  | 227  |
| 44 | 10 | - | 0.05   | 227  |
| 45 | 30 | - | 0.0025 | 227  |
| 46 | 30 | - | 0.01   | 227  |
| 47 | 30 | - | 0.025  | 227  |
| 48 | 30 | - | 0.05   | 227  |

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#### J. Compositions containing flavouring agents

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[0059] The following compositions were made up in propellant 227, with 0.1% w/w PVP/VA S-630.

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|    |   |                                   |
|----|---|-----------------------------------|
| 1. | Nedocromil sodium<br>peppermint oil       | 20mg/ml<br>0.1% w/w               |
| 2. | Nedocromil sodium<br>menthol<br>saccharin | 20mg/ml<br>0.05% w/w<br>0.03% w/w |
| 3. | Tipredane<br>menthol<br>saccharin         | 10mg/ml<br>0.05% w/w<br>0.03% w/w |

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#### K. Compositions containing additional excipients

55 [0060] The following composition was made up in propellant 227, to examine the effects of different excipients as valve lubricants.

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| a)                    |           |
|-----------------------|-----------|
| Nedocromil sodium     | 20mg/ml   |
| PVP/C30               | 0.1% w/w  |
| Lubricant             | 0.5% w/w  |
| Menthol               | 0.05% w/w |
| Saccharin, micronised | 0.03% w/w |
| Lubricants:           |           |
| PEG 200               |           |
| PEG 400               |           |
| PEG 600               |           |
| PEG 1000              |           |
| Miglyol 810           |           |
| Miglyol 829           |           |
| Miglyol 840           |           |
| Ethyl oleate          |           |
| Halocarbon oil 27     |           |
| Tyloxapol             |           |
| Polysorbate 80        |           |

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| b)                    |           |
|-----------------------|-----------|
| Nedocromil sodium     | 20mg/ml   |
| PVP (C30)             | 0.10% w/w |
| PEG 1500              | 0.20% w/w |
| Menthol               | 0.05% w/w |
| Saccharin, micronised | 0.03% w/w |

| c)          |          |           |
|-------------|----------|-----------|
| Tipredane   |          | 10.0mg/ml |
| PVP (C30)   |          | 0.10% w/w |
| Lubricant   |          | 0.50% w/w |
| Lubricants: | PEG 600  |           |
|             | PEG 1000 |           |

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| d)          |                                 |           |
|-------------|---------------------------------|-----------|
| Tipredane   |                                 | 10.0mg/ml |
| PVP (C30)   |                                 | 0.10% w/w |
| Lubricant   |                                 | 0.20% w/w |
| Lubricants: | PEG 600<br>PEG 1000<br>PEG 1500 |           |

**Claims****Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, MC, NL, PT, SE,**

20 1. A pressurized aerosol composition for administration by inhalation comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein, and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that said polymer is selected from the group consisting of polymers including recurring amide-containing structural units, polyvinylacetate and acrylic acid/methacrylic acid ester copolymers.

25 2. A composition according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.

30 3. A composition according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.

35 4. A composition according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.

5. A composition according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.

6. A composition according to Claim 2, wherein the polymer is a copolymer of amide-containing units and carboxylic acid ester units.

40 7. A composition according to Claims 6, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.

8. A composition according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.

45 9. A composition according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.

10. A composition according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate nedocromil sodium, tipredane, pentamidine isethionate, clemastine, acetyl- $\beta$ -methylcholine bromide and budesonide.

50 11. A process for the preparation of a composition according to Claim 1, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

55 **Claims for the following Contracting States : ES, GR**

1. A process for the preparation of a pressurized aerosol composition for administration by inhalation comprising a liq-

liquefied hydrofluoroalkane, a powdered medicament dispersable therein, and a polymer soluble in the liquefied hydrofluoroalkane, characterised in that said polymer is selected from the group consisting of polymers including recurring amide-containing structural units, polyvinylacetate and acrylic acid/methacrylic acid ester copolymers, which process comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

5        2. A process according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.

10      3. A process according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.

15      4. A process according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.

20      5. A process according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.

25      6. A process according to Claim 2, wherein the polymer is a copolymer of amide containing units and carboxylic acid ester units.

30      7. A process according to any one of Claim 6, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.

35      8. A process according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.

40      9. A process according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.

45      10. A process according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, clemastine, acetyl- $\beta$ -methylcholine bromide and budesonide.

#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, MC, NL, PT, SE,

35      1. Druckaerosol-Zusammensetzung zur Verabreichung durch Inhalieren mit einem verflüssigten Hydrofluoralkan, einem darin dispergierten, pulverförmigen Medikament und einem in dem verflüssigten Hydrofluoralkan löslichen Polymer, dadurch gekennzeichnet, dass das Polymer aus der Gruppe ausgewählt ist, die aus Polymeren mit wiederkehrenden, amidhaltigen Struktureinheiten, Polyvinylacetat und Acrylsäure/Methacrylsäureester-Copolymeren besteht.

40      2. Zusammensetzung nach Anspruch 1, wobei das Polymer wiederkehrende Struktureinheiten enthält, die eine Amidgruppe enthalten.

45      3. Zusammensetzung nach Anspruch 1 oder 2, wobei das Polymer wiederkehrende 1-Ethyl-pyrrolidin-2-on-Einheiten einschließt.

50      4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei das Polymer Polyvinylpyrrolidone ist.

55      5. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei das Polymer ein Copolymer ist, das wiederkehrende 1-Ethyl-pyrrolidin-2-on-Einheiten enthält.

60      6. Zusammensetzung nach Anspruch 2, wobei das Polymer ein Copolymer von amidhaltigen Einheiten und Carbonsäureester-Einheiten ist.

65      7. Zusammensetzung nach Anspruch 6, wobei das Polymer ein Polyvinylpyrrolidone/Vinylacetat-Copolymer ist.

70      8. Zusammensetzung nach Anspruch 1, wobei das Polymer Polyvinylacetat oder ein Copolymer von Acrylsäure- und

Methacrylsäureestern ist.

9. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei die Polymerkonzentration 0,00001 bis 10 %-Masse beträgt.
- 5 10. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei das Medikament aus einem oder mehreren der folgenden Medikamente ausgewählt ist: Terbutalinsulfat, Beclomethasondipropionat, Salbutamolsulfat, Fluticasondipropionat, Reproterolhydrochlorid, Fenoterolhydrobromid, Natriumcromoglycat, Nedocromilnatrium, Tipredan, Pentamidinisoethionat, Clemastin, Acetyl-β-methylcholinbromid und Budesonid.
- 10 11. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1, das das Dispergieren des pulverförmigen Medikaments und des Polymers in dem verflüssigten Hydrofluoroalkan umfasst.

**Patentansprüche für folgende Vertragsstaaten : ES, GR**

- 15 1. Verfahren zur Herstellung einer Druckaerosol-Zusammensetzung zur Verabreichung durch Inhalieren mit einem verflüssigten Hydrofluoroalkan, einem darin dispergierbaren, pulverförmigen Medikament und einem in dem verflüssigten Hydrofluoroalkan löslichen Polymer, dadurch gekennzeichnet, dass das Polymer aus der Gruppe ausgewählt ist, die aus Polymeren mit wiederkehrenden, amidhältigen Struktureinheiten, Polyvinylacetat und Acrylsäure/Methacrylsäureester-Copolymeren besteht, welches Verfahren das Dispergieren des pulverförmigen Medikaments und des Polymers in dem verflüssigten Hydrofluoroalkan umfasst.
- 20 2. Verfahren nach Anspruch 1, wobei das Polymer wiederkehrende Struktureinheiten enthält, die eine Amidgruppe enthalten.
- 25 3. Verfahren nach Anspruch 1 oder 2, wobei das Polymer wiederkehrende 1-Ethylen-pyrrolidin-2-on-Einheiten einschließt.
4. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Polymer Polyvinylpyrrolidon ist.
- 30 5. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Polymer ein Copolymer ist, das wiederkehrende 1-Ethylen-pyrrolidin-2-on-Einheiten enthält.
6. Verfahren nach Anspruch 2, wobei das Polymer ein Copolymer von amidhältigen Einheiten und Carbonsäureester-Einheiten ist.
- 35 7. Verfahren nach Anspruch 6, wobei das Polymer ein Polyvinylpyrrolidon/Vinylacetat-Copolymer ist.
8. Verfahren nach Anspruch 1, wobei das Polymer Polyvinylacetat oder ein Copolymer von Acrylsäure- und Methacrylsäureestern ist.
- 40 9. Verfahren nach einem der vorhergehenden Ansprüche, wobei die Polymerkonzentration 0,00001 bis 10 %-Masse beträgt.
- 45 10. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Medikament aus einem oder mehreren der folgenden Medikamente ausgewählt ist: Terbutalinsulfat, Beclomethasondipropionat, Salbutamolsulfat, Fluticasondipropionat, Reproterolhydrochlorid, Fenoterolhydrobromid, Natriumcromoglycat, Nedocromilnatrium, Tipredan, Pentamidinisoethionat, Clemastin, Acetyl-β-methylcholinbromid und Budesonid.

**50 Revendications**

**Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, MC, NL, PT, SE,**

- 55 1. Composition d'aérosol sous pression pour administration par inhalation, comprenant un hydrofluoroalcane liquéfié, un médicament pulvérulent qui y est dispersable et un polymère soluble dans l'hydrofluoroalcane liquéfié, caractérisée en ce que ledit polymère est choisi dans le groupe constitué de polymères comprenant des unités structurelles récurrentes contenant des amides, du poly(acétate de vinyle) et des copolymères d'esters d'acide acrylique et d'acide méthacrylique.

2. Composition selon la revendication 1, dans laquelle le polymère contient des unités structurelles récurrentes contenant un groupement amide.
3. Composition selon la revendication 1 ou 2, dans laquelle le polymère comprend des unités récurrentes de 1-éthylène-pyrrolidin-2-one.
4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle le polymère est la polyvinylpyrrolidone.
- 10 5. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle le polymère est un copolymère contenant des unités récurrentes de 1-éthylène-pyrrolidin-2-one.
6. Composition selon la revendication 2, dans laquelle le polymère est un copolymère d'unités contenant des amides et d'unités d'esters d'acides carboxyliques.
- 15 7. Composition selon la revendication 6, dans laquelle le polymère est un copolymère de polyvinylpyrrolidone et d'acétate de vinyle.
8. Composition selon la revendication 1, dans laquelle le polymère est le poly(acétate de vinyle) ou un copolymère d'esters d'acide acrylique et d'acide méthacrylique.
- 20 9. Composition selon l'une quelconque des revendications précédentes, dans laquelle la concentration du polymère est de 0,00001% à 10% en poids/poids.
- 25 10. Composition selon l'une quelconque des revendications précédentes, dans laquelle le médicament est choisi parmi un ou plusieurs des éléments suivants : le sulfate de terbutaline, le dipropionate de bêclométhasone, le sulfate de salbutamol, le propionate de fluticasone, le chlorhydrate de reprotérol, le bromhydrate de fénotérol, le cromoglycate de sodium, le nédocromil sodique, le tiprüdane, l'isoéthionate de pentamidine, la clémastine, le bromure d'acétyl-β-méthylcholine et le budésonide.
- 30 11. Procédé de préparation d'une composition selon la revendication 1, qui comprend la dispersion du médicament pulvérulent et du polymère dans de l'hydrofluoralcane liquéfié.

**Revendications pour les Etats contractants suivants : ES, GR**

- 35 1. Procédé de préparation d'une composition d'aérosol sous pression pour administration par inhalation, comprenant un hydrofluoralcane liquéfié, un médicament pulvérulent qui y est dispersable et un polymère soluble dans l'hydrofluoralcane liquéfié, caractérisé en ce que ledit polymère est choisi dans le groupe constitué de polymères comprenant des unités structurelles récurrentes contenant des amides, du poly(acétate de vinyle) et des copolymères d'esters d'acide acrylique et d'acide méthacrylique, ledit procédé comprenant la dispersion du médicament pulvérulent et du polymère dans l'hydrofluoralcane liquéfié.
- 40 2. Procédé selon la revendication 1, dans lequel le polymère contient des unités structurelles récurrentes contenant un groupement amide.
- 45 3. Procédé selon la revendication 1 ou 2, dans lequel le polymère comprend des unités récurrentes de 1-éthylène-pyrrolidin-2-one.
4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel le polymère est la polyvinylpyrrolidone.
- 50 5. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel le polymère est un copolymère contenant des unités récurrentes de 1-éthylène-pyrrolidin-2-one.
6. Procédé selon la revendication 2, dans lequel le polymère est un copolymère d'unités contenant des amides et d'unités d'esters d'acides carboxyliques.
- 55 7. Procédé selon la revendication 6, dans lequel le polymère est un copolymère de polyvinylpyrrolidone et d'acétate de vinyle.

8. Procédé selon la revendication 1, dans lequel le polymère est le poly(acétate de vinyle) ou un copolymère d'esters d'acide acrylique et d'acide méthacrylique.
- 5 9. Procédé selon l'une quelconque des revendications précédentes, dans lequel la concentration du polymère est de 0,00001% à 10% en poids/poids.
- 10 10. Procédé selon l'une quelconque des revendications précédentes, dans lequel le médicament est choisi parmi un ou plusieurs des éléments suivants : le sulfate de terbutaline, le dipropionate de bêclométhasone, le sulfate de salbutamol, le propionate de fluticasone, le chlorhydrate de reprotérol, le bromhydrate de fénotérol, le cromoglycate de sodium, le nédocromil sodique, le tiprédate, l'isoéthionate de pentamidine, la clémastine, le bromure d'acétyl-β-méthylcholine et le budésonide.

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